## Remarks

This amendment is being submitted in response to the Final Rejection mailed June 23, 2008 in connection with the above-identified application. A Notice of Appeal was filed, with an appropriate Petition for Extension of Time, on December 18, 2008. Therefore, this filing, which is being made concurrently with a Petition for a Four-Month Extension and a Request for Continued Examination, is timely as it is being made on or before June 18, 2009.

## Amendment

Claim 25 has been amended to change the phrase "the CpG immunity adjuvant" to "a CpG immunity adjuvant." No new matter has been added.

## Provisional Obviousness-Type Double-Patenting Rejections

The Examiner has imposed a number of provisional, obviousness-type double patenting rejections, over the claims of co-pending Application Serial Nos. 11/915,044 and 11/735,319. In addition, the Examiner had withdrawn a previously imposed provisional obviousness-type double rejection over Serial No. 11/135,660 because that application had been held abandoned by the PTO. However, the '660 Application has been revived, and it is assumed that that provisional obviousness-type double patenting rejection would/will be re-imposed.

Because each of the obviousness-type double patenting rejections is provisional, applicants cannot yet respond to them by filing a terminal disclaimer, or otherwise. None of the claims in this application or any of the cited applications have yet been indicted as being allowable. Accordingly, Applicants cannot yet file a Terminal Disclaimer, as it is not yet known in which application the Terminal

Disclaimer would have to be filed, or whether a Terminal Disclaimer would be required (depending on the scope of the allowed claims). Applicants are not seeking to defer responding to these rejections. However, any response would be premature unless and until the claims in this application and/or the other applications are indicated as allowable.

**Rejection under 35 U.S.C. § 112**

The Examiner has rejected claim 25 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants understand that the Examiner is concerned that it was unclear what was being referred to by the phrase "the CpG immunity adjuvant." Applicants have obviated this rejection by amending claim 25 to recite --a CpG immunity adjuvant.-- Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

**Rejection under 35 U.S.C. § 102(b)**

The Examiner has rejected claims 1-3 and 21-25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Zagury, et al., WO 02/011759 A1 ('Zagury"). According to the Examiner, in the January 23, 2007 Office Action:

> "Zagury et al., teach immunogenic compositions with an anti-cytokine effect comprising an immunogen, including TNFα conjugated to a carrier protein, including KLH...The immunogenic complex of KLH and TNFα is taught using glutaraldehyde at p. 22..."

(Office Action, p. 14). Applicants traverse this rejection.

As discussed in the January 31, 2008 Amendment, Zagury only discloses conjugates wherein the antigenic protein is exclusively linked to the carrier protein by covalent bonding (100%). Thus, Zagury does not anticipate the claimed invention,

which requires that more than 1% and less than 40% of the TNFα proteins be covalently linked to KLH carrier protein molecules.

In response to this argument, the Examiner wrote that "this assertion is testable" and that in the absence of evidence "the TNFα-KLH conjugates taught by [Zagury] inherently comprise more than 1% and less than 40$ of TNFα proteins...covalently lined to the KLH carrier protein" (Final Rejection, p. 5). In response, Applicants provide herewith the Rule 132 Declaration of Dr. Daniel Zagury ("Zagury Declaration"), which provides the evidence requested by the Examiner. Dr. Zagury is the lead inventor on the Zagury reference cited by the Examiner. The Zagury Declaration is attached hereto as Exhibit A.

First, as indicated previously, there is no disclosure in Zagury of an immunogenic compound comprising both TNFα protein molecules and KLH carrier protein molecules (Zagury Decl. ¶ 7). There are numerous vaccines exemplified in Zagury, but none of them comprise TNFα-KLH conjugates (Zagury Decl. ¶¶ 8-10).

Second, contrary to the Examiner's contention, Zagury Paragraph [0134] does not support the proposition that "glutaraldehyde is taught as the preferred bifunctional coupling reagent in an anti-TNFα vaccine conjugate." Paragraph [0134] of Zagury relates to the preparation of a TNFα immunogen comprising (i) a step of treatment of TNFα with formaldehyde, and then (ii) a step of treatment of the product resulting from step (i) with glutaraldehyde, in accordance with the protocol described in Zagury for the p53 immunogen (Zagury Decl., ¶ 14). That protocol involves detoxification of the p53 immunogen with formaldehyde, followed by reaction of the detoxified antigen with glutaraldehyde, before blocking the excess aldehyde groups with glycine. (Zagury Decl., ¶ 15). Accordingly, the procedure for preparing the p53 immunogen does not include a step of coupling p53 with KLH; therefore Zagury Paragraph [0134]

cannot and does not disclose a preparation of a TNFα immunogen with KLH, nor is it aimed at such a preparation (Zagury Decl. ¶¶ 16-17).

In fact, the glutaraldehyde is used in the procedure of Paragraph [0134] as bridging agent for generating intra- and inter-molecular covalent bonds in the TNFα molecules in order to stabilize the immunogenic product, not to couple TNFα to other molecules of interest. (Zagury Decl., ¶ 18).

Finally, it is important to note that the last step of the procedure of Paragraph [0134] - adding glycine to block any unreacted glutaraldehyde functionality to ensure that the final immunogenic product is chemically inert – ensures that the product could not be coupled to KLH, even is such coupling were desired (Zagury Decl. ¶ 19).

Third, the conjugates actually prepared by Zagury between the antigenic proteins of interest (VEGF, E7 or IFNα) and KLH were prepared in such a way that the antigenic protein and KLH are linked exclusively or essentially exclusively through covalent bonds (and thus would be outside the scope of pending claim 1, even if the TNFα antigen were used) (Zagury Decl., ¶ 20). The method disclosed by Zagury has four essential steps, which are the same for each of the antigenic proteins, though VEGF is the one identified here:

(1) preparing a KLH protein that is activated by glutaraldehyde by reacting the said KLH protein with glutaraldehyde and then eliminating the excess of unreacted glutaraldehyde by dialysis;

(2) adding the VEGF protein to the previously prepared glutaraldehyde-activated KLH, so as to generate covalent bonds between (i) the free aldehyde groups present on the glutaraldehyde-activated KLH and (ii) the VEGF molecules, and then;

(3) blocking the unreacted free aldehyde groups by adding glycine, before

(4) purifying the resulting mixture by size exclusion chromatography, so as to remove the unreacted VEGF and KLH molecules.

(Zagury Decl., ¶ 21)

This method results in the production of immunogenic conjugates where the antigenic proteins are covalently bound to the KLH molecules because the antigenic protein molecules are reacted with activated KLH, which means that the only possible point of attachment is by chemical reaction with the free aldehyde groups on the activated KLH (Zagury Decl., ¶ 23). Moreover, any antigenic protein molecules not covalently bound to the KLH are separated from the covalent conjugate product during the final size exclusion chromatography step (Id.)

Thus, Zagury's method of preparation could not result in a conjugate which fell within the scope of the present claims.

This analysis is further supplemented by experimental work carried out by Dr. Zagury. In that work, Dr. Zagury prepared an immunogenic conjugate between TNFα and KLH using the Zagury's method, except that the final size exclusion chromatography step was not performed (Zagury Decl., ¶ 32). Dr. Zagury also prepared a TNFα-KLH conjugate using the method disclosed in Example 9 of the present application (Id.).

As discussed in detail in the Zagury Declaration, Dr. Zagury's work shows conclusively that in the TNFα-KLH conjugate produced using the Zagury method, all of the TNFα is covalently bound to the KLH (Zagury Decl., ¶¶ 33-38): "[I]n a conjugate compound prepared according to Zagury, the TNFα molecules are all covalently bound to the KLH molecules" (Zagury Decl., ¶ 39, emphasis added). Therefore, conjugates prepared according to the teachings of Zagury cannot anticipate the present claims.

Dr. Zagury also performed experimental work which showed that the TNFα in conjugates prepared according to the present invention is coupled to the KLH in a different way than TNFα in conjugates prepared according to Zagury's method (Zagury Decl., ¶¶ 42-56).

Finally, Dr. Zagury also performed experimental work which demonstrates that the immunogenic conjugates of the present invention have a far greater immunogenicity than the conjugate prepared with Zagury's method (Zagury Decl., ¶¶ 58-67).

In conclusion, the information and evidence from the Zagury Declaration shows that the structural features of the conjugates according to the invention are clearly distinguishable from the conjugates prepared according to Zagury's methods and have superior immunogenic properties (Zagury Decl. ¶¶ 68-70). Accordingly, applicants respectfully submit that the anticipation rejection of the claims over Zagury should be reconsidered and withdrawn.

**Conclusion**

Applicant respectfully submits that the claims are in condition for allowance, and earnestly solicits prompt notice to that effect. If the Examiner believes that a personal interview or telephone call could advance prosecution of this application, please contact the undersigned.

Respectfully submitted,
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